IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Richard Franklin
Serial No.:	10/762,566
For:	FORMULATION AND METHODS FOR THE TREATMENT OF THROMBOCYTHEMIA
Filed:	January 23, 2004
Examiner:	Alicia R. Hughes
Art Unit:	1614

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CERTIFICATE OF ELECTRONIC FILING

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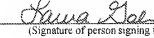

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APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

As required under 37 C.F.R. § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on September 8, 2010, and is in furtherance of said Notice of Appeal.

The fees required under 37 C.F.R. § 41.20(b)(2) accompany this APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

I.	Real Party In Interest
II.	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments
V.	Summary of Claimed Subject Matter
VI.	Grounds of Rejection to be Reviewed on Appeal
VII.	Argument
VIII.	Claims Appendix
IX.	Evidence Appendix
X.	Related Proceedings Appendix

I. REAL PARTY IN INTEREST

The real party in interest is Shire Biopharmaceuticals Holdings Ireland Limited, the assignee of record, which is a subsidiary of Shire plc.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which are related to, will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 9 claims pending in the application.

B. Current Status of Claims

1. Claims cancelled: 1, 3-11, 14-16, and 23-50
2. Claims withdrawn from consideration but not cancelled: None
3. Claims pending: 2, 12, 13, and 17-22
4. Claims allowed: None
5. Claims rejected: 2, 12, 13, and 17-22
6. Claims objected to: None

C. Claims on Appeal

The claims on appeal are claims 2, 12, 13, and 17-22.

IV. STATUS OF AMENDMENTS

The present Appeal Brief is filed in response to the Final Office Action mailed June 8, 2010. No amendments were filed after the Final Office Action. A list of the appealed claims is found in Section VIII, the Claims Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 2 recites a method of treating thrombocythemia by administering a skin permeable form of anagrelide or a pharmaceutically acceptable salt of anagrelide in an amount effective to treat thrombocythemia. *See, e.g.*, the abstract, page 3, lines 16-26, page 5, lines 5-10 and 19-24, page 10, lines 4-18, page 13, lines 18-28, and page 20, lines 4-27 of the specification as filed. Claim 2 further recites that the anagrelide or salt thereof is administered transdermally. *See, e.g.*, page 3, lines 5-6, page 6, lines 11-12, and Examples 1-7 from page 28, line 4 to page 30, line 18 of the specification as filed. Claim 2 also recites that the anagrelide or salt thereof is transdermally administered to minimize first pass liver metabolism thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent amount of anagrelide. *See, e.g.*, page 2, lines 27-29, page 4, line 30 to page 5, line 4, page 5, lines 26 to page 6, line 3, in Example 8 starting on page 30, line 20, and in Example 11 starting on page 34, line 9 of the application as filed. The structure of "Metabolite A," described in Example 11 as producing cardiovascular side effects, is provided on page 31 in Example 8 and has the chemical name "3-hydroxy anagrelide." Thus, "3-hydroxy anagrelide" can be substituted for the phrase "metabolites exhibiting cardiovascular and/or inotropic side effects" disclosed on page 5, lines 30-31.

The remainder of the claims (*i.e.*, claims 12, 13, and 17-22) depends from claim 2.

Dependent claim 12 sets forth that the thrombocythemia is associated with essential thrombocythemia (ET), chronic myologenous leukemia (CML), polycythemia vera (PV), agnogenic myeloid metaplasia (AMM) or sickle cell anemia (SCA). *See, e.g.*, page 1, line 26 to page 2, line 2 and page 13, lines 4-6 of the specification as filed.

Dependent claim 13 recites that the anagrelide or salt thereof is administered in an amount of 0.1 to 20 mg/kg/day. *See, e.g.*, page 7, lines 8-10, page 14, line 15-17, Example 11 starting on page 35, line 22, and Example 12 starting on page 36, line 23 of the specification as filed.

Dependent claim 17 recites that the anagrelide or salt thereof is in the form of a composition which further comprises at least one skin permeation enhancer. *See, e.g.*, page 7, lines 25-27, page 17, line 30 to page 18, line 5, and page 19, lines 1-17 of the specification as filed.

Dependent claim 18 sets forth that the at least one skin permeation enhancer of claim 17 is linalool, carvacrol, thymol, citral, menthol, oleic acid, or t-anethole. *See, e.g.*, page 21, line 3, page 23, lines 10-24, and page 30, line 14 of the specification as filed.

Dependent claim 19 recites that the administration of anagrelide or salt thereof is via a transdermal patch having a single-layer drug-in-adhesive system comprising a composition containing the anagrelide or anagrelide salt, one or more excipients, and at least one skin-contacting adhesive, which is combined with a single backing film. *See, e.g.*, page 7, line 29 to page 8, line 3, page 15, lines 9-13, and page 18, lines 13-21 of the specification as filed. Backing layers are described on page 16, lines 11-17 of the specification as filed. Adhesives are disclosed from page 16, line 18 to page 17, line 28.

Dependent claim 20 sets forth that the administration of anagrelide or salt thereof is via a transdermal patch having a multi-layer drug-in-adhesive system wherein: (a) said system comprises at least two distinct layers comprising the anagrelide or anagrelide salt and at least one adhesive, and a membrane between said at least two layers or (b) said system comprises at least two distinct layers comprising the anagrelide or anagrelide salt and at least one adhesive, and a single backing film. *See, e.g.*, page 8, lines 5-13, page 15, lines 15-19, and page 18, lines 13-21 of the specification as filed. Backing layers are described on page 16, lines 11-17 of the specification as filed. Adhesives are disclosed from page 16, line 18 to page 17, line 28.

Dependent claim 21 recites that the administration of anagrelide or salt thereof is via a transdermal patch having a reservoir transdermal system comprising a liquid compartment containing a solution or suspension of the anagrelide or anagrelide salt, a release liner, and between said release liner and said liquid compartment, a semi-permeable membrane and at least one adhesive. *See, e.g.*, page 8, lines 15-20, page 15, lines 21-27, page 18, lines 13-21, and Examples 1, 2, and 4 on page 28, lines 4-24 and page 39, lines 6-13 of the specification as filed. Adhesives are disclosed from page 16, line 18 to page 17, line 28.

Dependent claim 22 sets forth that the administration of anagrelide or salt thereof is via a transdermal patch having a matrix system comprising a semisolid matrix containing a solution or suspension of the anagrelide or anagrelide salt which is in direct contact with a release liner, and a skin adhesion component incorporated in an overlay which forms a concentric configuration around said semisolid matrix. *See, e.g.*, page 8, lines 22-28, page 15, line 28 to page 16, line 2, and page 18, lines 13-21 of the specification as filed. Adhesives are disclosed from page 16, line 18 to page 17, line 28.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 2, 12, 13, and 17-20 are unpatentable under 35 U.S.C. § 103(a) as obvious over Lang in view of Miranda, D'Angelo, and Solberg, as evidenced by Bonkovsky and Ammar.[1]

2. Whether claims 21 and 22 are unpatentable under 35 U.S.C. § 103(a) as obvious over Lang in view of D'Angelo and Ferrini[2].

[1] The full citations of these references is as follows: U.S. Patent No. 6,194,420 ("Lang"); U.S. Patent No. 6,221,383 ("Miranda"); U.S. Patent No. 6,024,975 ("D'Angelo"); Solberg, *Seminars in Oncology*, Vol. 28, Issue 3, Supplement 10, page 10-15 (2002) ("Solberg"); Bonkovsky *et al.*, *Zakim and Boyer's Hepatology, 5th Edition*, pages 503-550 (2006) ("Bonkovsky"); and Ammar *et al.*, *International Journal of Pharmaceutics*, Vol. 327, pages 81-88 (2006) ("Ammar").

[2] Ferrini is U.S. Patent No. 5,133,972.

VII. ARGUMENT

1. Claims 2, 12, 13, and 17-20 are patentable over Lang in view of Miranda, D'Angelo, and Solberg, as evidenced by Bonkovsky and Ammar.

Claims 2, 12, 13, and 17-20 were rejected under 35 U.S.C. § 103(a) as obvious over Lang in view of Miranda, D'Angelo, and Solberg, as evidenced by Bonkovsky and Ammar.

Claim 2 recites a method of treating thrombocythemia by transdermally administering anagrelide or salt thereof. Claims 12, 13, and 17-20 depend from claim 2.

The presently claimed invention would not have been obvious because the cited combination of elements would have yielded more than a predictable use of prior art elements according to their established function. *See KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) and MPEP §2141(I). Prior to Applicant's invention, one of ordinary skill in the art could not have predicted that the cardiovascular side-effects observed in patients who are orally administered anagrelide would be minimized in a patient transdermally administered. The prior art neither discloses nor suggests a positive correlation between avoiding the first pass liver metabolism of anagrelide using transdermal administration and the disappearance of adverse cardiovascular side-effects. To the contrary, as discussed below, first pass liver metabolism is associated with detoxification.

Surprisingly, however, Applicant discovered that transdermally administering anagrelide to treat thrombocythemia as recited in the claims minimizes the adverse cardiovascular side-effects observed when anagrelide is administered orally. These unpredictable results are discussed in the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Richard Franklin ("the Franklin Declaration") filed September 19, 2007.

Dr. Franklin's Declaration explains that Applicant determined the surprising cause of the adverse cardiovascular side-effects: the metabolite 3-hydroxy anagrelide. *See* ¶7 of the Franklin Declaration. Prior to the present invention it was unknown that the severity of anagrelide's cardiovascular side effects was due to the 3-hydroxy metabolite. These side effects are not

trivial. A large number of patients orally treated with anagrelide fail to tolerate the drug. *See* ¶7 of the Franklin Declaration. The side effects of a drug can be due to a number of causes including the drug itself interacting with (unintended) receptors in the body. Without knowing the cause, a skilled artisan would not have known whether the cardiovascular side effects could be reduced, or how to do so. *See Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 67-68 (1923) (Eibel discovered that defects in a newsprint paper making machine could be removed by changing the speed of the stock used to make the paper by using gravity. The Supreme Court found that Eibel discovered the problem that caused defective paper, and he then used known principles to fix that problem, stating that "[t]he invention was not the mere use of a high speed or substantial pitch to remedy a known source of trouble. It was the discovery of the source not before known, and the application of the remedy, for which Eibel was entitled to be rewarded in his patent.").

The transdermal administration of anagrelide for treating thrombocythemia as recited in the pending claims reduces adverse cardiovascular side-effects compared to patients orally administered anagrelide by minimizing the amount of 3-hydroxy anagrelide formed during first-pass liver metabolism thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to the plasma concentration of 3-hydroxy anagrelide after the oral administration of anagrelide. The reduction in the plasma concentration of 3-hydroxy anagrelide reduces the inhibition of phosphodiesterase III (PDEIII, an enzyme known to affect the cardiovascular system) by 3-hydroxy anagrelide resulting in the reduction in the adverse cardiovascular side-effects. Dr. Franklin's Declaration provides 2 reasons for the non-obviousness of Applicant's invention. *See* ¶8 of the Franklin Declaration. First, 3-hydroxy anagrelide inhibited PDEIII to a greater than expected degree in view of the relatively minor change to the structure of anagrelide (*i.e.*, 3-hydroxy anagrelide inhibited PDEIII 40 times more potently than anagrelide). Second, the fact that the 3-hydroxy anagrelide metabolite causes undesirable side-effects represents the opposite of the expected metabolic detoxification process occurring in the liver.

See also the Citizen Petition dated August 13, 2004 related to anagrelide (*e.g.*, the 3rd complete paragraph on page 8 stating that 3-hydroxy anagrelide is the likely cause of the cardiovascular side-effects observed after the administration of anagrelide and the 4th paragraph on page 11 summarizing that 3-hydroxy anagrelide is formed by first pass liver metabolism,

Exhibit 1 submitted on March 28, 2008); the section entitled "Pharmacological Properties" on page 113 of Wagstaff and Keating, *Drugs* 2006, 66:111-131 (the 3-hydroxy anagrelide metabolite is 40 times more potent than anagrelide as an inhibitor of PDEIII resulting in inotropic effects and systemic exposure to 3-hydroxy anagrelide is about twice of the parent in patients with thrombocythemia, Exhibit 2 submitted on March 28, 2008); the abstract of Wang *et al., British Journal of Pharmacology* 2005, 146:324-332 (3-hydroxy anagrelide (*i.e.*, BCH24426) is 40 times more potent than anagrelide as an inhibitor of PDEIII, Exhibit 3 submitted on March 28, 2008).

Notwithstanding the Examiner's assertion that the prior art generally discloses the reduction in first pass liver metabolism by transdermal administration, none of the cited references, taken separately or together, disclose or suggest that the severity of the cardiovascular side effects of anagrelide are due to its 3-hydroxy metabolite. This unexpected result, discovered by Applicant, makes the claimed invention of transdermally administering anagrelide to treat thrombocythemia non-obvious.

The Examiner asserts on pages 4 and 5 of the Office Action mailed June 8, 2010 that the recitation "thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent amount of anagrelide" in claim 2 is a function that necessarily flows from the method claimed and cites to *Atlas Powder Co. v. Ireco Inc.*, 190 F. 3d 1342, 1347 (Fed. Cir. 1999) to argue that discovering a new property of an old method does not make the old method patentable. The Examiner contends that Applicant must provide evidence that the prior art method does not possess the characteristics relied upon by the presently claimed invention citing to *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

The Examiner's reliance on *Atlas Powder* and *In re Fitzgerald* is misguided. In *Atlas Powder*, the patent at issue was held invalid as being anticipated by a prior art reference because although the reference did not expressly disclose one of the patent limitations, the reference disclosed each of the other limitations of the claims and the non-expressly disclosed limitation was inherent in the prior art disclosure. *Atlas Powder*, 190 F.3d at 1347-1350. Similar to *Atlas Powder*, the court in *In re Fitzgerald* considered whether appellants' claimed fasteners would have been unpatentable over Barnes, the primary prior art reference, which disclosed identical or

nearly identical fasteners, but did not explicitly disclose the claimed functional crystallization shrinkage limitation. *In re Fitzgerald*, 619 F.2d 67 at 70-71. *See also* MPEP § 2112(V). The Appellants did not supply sufficient evidence that the Barnes fasteners were different from the claimed fasteners and, thus, the court upheld the rejection. *Id.* at 71.

In *Atlas Powder* and *In re Fitzgerald*, the claims were held unpatentable because a single cited reference disclosed each of the limitations of the claimed invention except for a claim limitation that was inherent in the reference. Unlike *Atlas Powder* and *In re Fitzgerald*, each of the references cited by the Examiner in the present application is missing more than just an inherent feature recited in the claims. No single cited reference discloses the treatment of thrombocythemia by transdermally administering skin permeable anagrelide:

- Lang teaches the use of anagrelide to treat thrombocythemia, but not routes of administration for anagrelide.
- Miranda discloses the transdermal use of anagrelide, as one drug in a list of over a dozen, to treat thrombosis, however the use of anagrelide to treat thrombocythemia is not disclosed or suggested.
- D'Angelo describes a transdermal drug delivery system, but does not disclose or suggest anagrelide or the treatment of thrombocythemia.
- Solberg discloses the treatment of thrombocythemia by administering anagrelide and its associated cardiovascular side-effects, but does not disclose or suggest the transdermal delivery of anagrelide.
- Bonkovsky, a chapter entitled "Drug-Induced Liver Injury" from a textbook entitled "A Textbook of Liver Disease," discloses anagrelide as a cardiovascular drug that is not reported to cause significant liver injury (*see* Table 26-13), but neither discloses nor suggests the treatment of thrombocythemia using transdermally administered anagrelide. Consistent with Dr. Franklin's arguments in his Declaration, the liver "function[s] to remove potentially toxic compounds from organisms." *See* the first paragraph of the Introduction.
- Ammar teaches the transdermal delivery of aspirin as a potential way to reduce the gastrointestinal side effects of orally administered aspirin. *See* the abstract and section 3.3 on

page 86 of Ammar. Ammar discloses that aspirin is an antithrombic used to reduce the risk of cardiovascular disease. *See* the abstract of Ammar. Ammar does not teach or suggest the treatment of thrombocythemia using transdermally administered anagrelide. Moreover, Ammar does not teach or suggest (1) the treatment of thrombocythemia using aspirin as asserted by the Examiner in the 2nd sentence in the first complete paragraph on page 4 of the Office Action mailed June 8, 2010 or (2) the reduction in cardiovascular side effects by transdermal administration as suggested by the Examiner in the last sentence in the first complete paragraph on page 4 of the Office Action mailed June 8, 2010.

Hence, the Examiner combines **several** prior art references to asset the obviousness of the pending claims and then contends that the claims are obvious because the recitation "thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent amount of anagrelide" in claim 2 is inherent to the claimed method. *See* pages 4-5 of the Office Action mailed June 8, 2010.

However, that which is inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejecting the claimed invention as obvious. *See In re Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977) (the claimed method of using certain dosages of adamantine compounds to curb appetite was not obvious over the prior art teaching structurally similar compounds for use as antiviral agents at the same dosages contrary the PTO's argument that appellant's appetite curbing amount of compound would inherently achieve appetite curbing when administered as an antiviral agent); *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966). Applying the law to this application, the reduction in cardiovascular side-effects caused by the 3-hydroxy anagrelide metabolite cannot serve as a proper basis for finding obviousness because this result was not known at the time of the invention. Instead, Applicant discovered this unexpected feature of the claimed invention.

Moreover, the obviousness rejection is invalid because Bonkovsky and Ammar are not prior art. Both references were published in 2006 after the January 23, 2004 filing date of the present application.

Accordingly, Applicant respectfully requests withdrawal of the obviousness rejection.

2. Claims 21 and 22 are patentable over Lang in view of D'Angelo and Ferrini.

Claims 21 and 22 were rejected under 35 U.S.C. § 103(a) as obvious over Lang in view of D'Angelo and Ferrini.

Claims 21 and 22 depend from claim 2 and set forth that the anagrelide is administered via a transdermal patch.

Claims 21 and 22 would not have been obvious for the same reasons that claims 2, 12, 13, and 17-20 as discussed above would not have been obvious.

First, the claims are more than a predictable use of prior art elements according to their established function. Unexpectedly, the treatment of thrombocythemia by transdermally administering anagrelide minimizes the cardiovascular side-effects observed when anagrelide is orally administrated.

Second, the inherency of this unexpected feature is not a basis for rejecting the claimed invention as obvious. Ferrini, like each of the other cited references, is missing more than just an inherent feature which is expressly recited in the claims. Ferrini describes the transdermal administration of methanediphosphonic acid derivatives, but does not disclose or suggest anagrelide or the treatment of thrombocythemia.

Finally, although not cited at the beginning of the rejection on page 6 of the Office Action mailed June 8, 2010, the Examiner seems to incorporate Bonkovsky, Ammar, and Solberg into the rejection according to the last paragraph on page 6 of the Office Action. The rejection is also improper because Bonkovsky and Ammar are not prior art.

For at least these reasons, Applicant respectfully requests withdrawal of the obviousness rejection.

Dated: November 5, 2010

Respectfully submitted,

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Attachments: VIII. Claims Appendix
IX. Evidence Appendix containing tabs (a)-(d)
X. Related Proceedings Appendix

VIII. CLAIMS APPENDIX

Claims Involved in the Appeal of Application Serial No. 10/762,566

1. (Canceled)

2. (Previously Presented) A method for the treatment of thrombocythemia in a patient with thrombocythemia comprising transdermally administering to said patient a skin permeable form of anagrelide or a pharmaceutically acceptable salt of anagrelide in an amount effective to treat thrombocythemia to minimize first pass liver metabolism thereby reducing the plasma concentration of 3-hydroxy anagrelide compared to a patient orally administered the equivalent amount of anagrelide.

3.-11. (Canceled)

12. (Previously Presented) The method according to claim 2, wherein said thrombocythemia is associated with essential thrombocythemia (ET), chronic myologenous leukemia (CML), polycythemia vera (PV), agnogenic myeloid metaplasia (AMM) or sickle cell anemia (SCA).

13. (Previously Presented) The method according to claim 2, wherein the anagrelide or anagrelide salt is administered in an amount of 0.1 to 20 mg/kg/day.

14.-16. (Canceled)

17. (Previously Presented) The method according to claim 2, wherein the anagrelide or anagrelide salt is in the form of a composition which further comprises at least one skin permeation enhancer.

18. (Previously Presented) The method according to claim 17, wherein said at least one skin permeation enhancer is linalool, carvacrol, thymol, citral, menthol, oleic acid, or t-anethole.

19. (Previously Presented) The method according to claim 2, wherein administration is via a transdermal patch having a single-layer drug-in-adhesive system comprising a composition containing the anagrelide or anagrelide salt, one or more excipients, and at least one skin-contacting adhesive, which is combined with a single backing film.

20. (Previously Presented) The method according to claim 2, wherein administration is via a transdermal patch having a multi-layer drug-in-adhesive system wherein: (a) said system comprises at least two distinct layers comprising the anagrelide or anagrelide salt and at least one adhesive, and a membrane between said at least two layers or (b) said system comprises at least two distinct layers comprising the anagrelide or anagrelide salt and at least one adhesive, and a single backing film.

21. (Previously Presented) The method according to claim 2, wherein administration is via a transdermal patch having a reservoir transdermal system comprising a liquid compartment containing a solution or suspension of the anagrelide or anagrelide salt, a release

liner, and between said release liner and said liquid compartment, a semi-permeable membrane and at least one adhesive.

22. (Previously Presented) The method according to claim 2, wherein administration is via a transdermal patch having a matrix system comprising a semisolid matrix containing a solution or suspension of the anagrelide or anagrelide salt which is in direct contact with a release liner, and a skin adhesion component incorporated in an overlay which forms a concentric configuration around said semisolid matrix.

23.-50. (Canceled)

IX. EVIDENCE APPENDIX

The following evidence is cited in the Appeal Brief and copies of which are supplied in this appendix:

(a) the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Richard Franklin ("the Franklin Declaration") filed as part of a response dated September 19, 2007 which was entered[3] by the Examiner according to pages 2 and 3 of the Office Action mailed January 28, 2008;

(b) the Citizen Petition dated August 13, 2004 submitted as Exhibit 1 to a response dated March 28, 2008 which entered by the Examiner according to page 2 of the Office Action mailed April 16, 2008;

(c) Wagstaff and Keating, *Drugs* 2006, 66:111-131 submitted as Exhibit 2 to a response dated March 28, 2008 which entered by the Examiner according to page 2 of the Office Action mailed April 16, 2008; and

(d) Wang *et al.*, *British Journal of Pharmacology* 2005, 146:324-332 submitted as Exhibit 3 to a response dated March 28, 2008 which entered by the Examiner according to page 2 of the Office Action mailed April 16, 2008.

[3] Although the Examiner did not explicitly state that the response dated September 19, 2007 was entered, she acknowledged that Applicant cancelled claims in this response as well as acknowledged the receipt of the Franklin Declaration.

X. RELATED PROCEEDINGS APPENDIX

No related proceedings are referenced in II. above, hence copies of decisions in related proceedings are not provided.